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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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ROBINS & PASTERNAK
1731 EMBARCADERO ROAD
SUITE 230
PALO ALTO, CA 94303

EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 03/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/855,342	CALIGIURI ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 Augsut 2005 and 23 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 5, 2005, has been entered.

1. The amendment filed January 23, 2006, is acknowledged and has been entered, in part.

2. The amendment filed August 5, 2005, has been entered. Claims 12, 16, 17, 24, 25, 27, 30, 31, 41, 42, 53, 56, 59, and 62 have been amended. Claims 63-73 have been added.

3. Claims 12-73 are pending in the application and are currently under prosecution.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Amendments

5. In response to the amendment filed January 23, 2006, Applicant is reminded that in correcting non-compliant amendments, *only* a corrected copy of the section of the amendment, in its entirety, which was found deficient should be provided.

It is presumed that apart from correcting the deficiency indicated in the Office communication mailed January 12, 2006, the amendment filed January 23, 2006, is a duplicate of the prior non-compliant amendment filed August 5, 2005, as no differences

were immediately obvious to the Examiner and Applicant does not appear to have pointed to any particular changes relative to the prior non-compliant amendment.

Only the "amendment to the specification" section of the amendment filed January 23, 2006, has been entered.

The claim set filed with the amendment of August 5, 2005, is that which has been used during the examination; if Applicant intended the claim set filed with the amendment of January 23, 2006, to replace the prior claim set, Applicant should advise the Examiner of such intention in replying to this Office action and point out any changes made in that version of the claims relative to their prior version, as filed with the amendment of August 5, 2005.

6. The amendment filed August 5, 2005, is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material, which appears not supported by the original disclosure, is the reference to "SEQ ID NO: 1" that has been inserted by the amendment to the specification at page 29, and the Sequence Listing disclosing the amino acid sequence of SEQ ID NO: 1.

As amended at page 29 in the paragraph beginning in line 2, the specification reads:

> The IL-2 formulation in this study is manufactured by Chrion Corporation of Emeryville, California, under the tradename Proleukin. The IL-2 in this formulation is a recombinantly produced human IL-2 mutein, called aldesleukin (SEQ ID NO:1), which differs from the native human IL-2 sequence in having the initial alanine residue eliminated and the cysteine residue at position 125 replaced by serine (referred to as des-alanyl-1, serine-125 human interleukin-2). This IL-2 mutein is expressed from E. coli, and subsequently purified by diafiltration and cation exchange chromatography as described in U.S. Patent No. 4,931,543.

Thus, the introduction of SEQ ID NO: 1 at page 29 by the amendment defines aldesleukin (i.e., des-alanyl-1, serine-125 human interleukin-2, or Proleukin™) as a polypeptide comprising SEQ ID NO: 1. Notably, the original disclosure at page 29 provides no apparent nexus between the amino acid sequence set forth as SEQ ID NO: 1 and aldesleukin (i.e., des-alanyl-1, serine-125 human interleukin-2, or Proleukin™).

At page 21, paragraph 2, of the amendment filed August 5, 2005, Applicant has asserted that the specification, as originally filed, provide support for this amendment to the specification, since "[t]his sequence is disclosed in Fig. 15b of U.S. Patent No. 4,518,584, which patent was incorporated by reference in the present specification, for example, at page 17, line 21. The disclosure at page 17 referring to U.S. Patent No. 4,518,584 reads, "the recombinant IL-2 muteins described in European Patent Application No. 83306221.9, filed Oct. 13, 1983 (published May 30, 1984 under No. 109748), which is the equivalent to Belgian Patent No. 893,016; U.S. Patent No. 4,518,584". This disclosure, however, does not appear to provide a nexus between the amino acid sequence set forth as the amino acid sequence depicted in Figure 15b of U.S. Patent No. 4,518,584 (i.e., SEQ ID NO: 1) and aldesleukin (i.e., des-alanyl-1, serine-125 human interleukin-2, or Proleukin™).

This issue might be resolved if Applicant were to point to particular disclosures in the specification, including the claims, as originally filed, which are believed to provide written support for the amendment to the specification, namely a nexus between the sequence depicted in Figure 15b of U.S. Patent No. 4,518,584, which has been incorporated by a reference to the patent at page 17 of the originally filed specification, and the primary structure (i.e., amino acid sequence) of Proleukin™ (aldesleukin).

Otherwise, it is duly noted that at page 17, lines 22-25, the specification teaches, "the IL-2 mutein (des-alanyl-1, serine-125 human interleukin-2) used in the examples herein and described in U.S. Patent No. 4,931,543, as well as other IL-2 muteins described in this U.S. Patent; all of which are herein incorporated by reference". If the sequence of des-alanyl-1, serine-125 human interleukin-2 is disclosed in U.S. Patent No. 4,931,543, perhaps this patent may provide support for the inclusion of the reference to SEQ ID NO: 1 at page 29.

Applicant is required to remedy this issue by amending the specification to delete the reference to SEQ ID NO: 1 at page 29 and cancel the Sequence Listing disclosing SEQ ID NO: 1, or to otherwise resolve this issue by pointing to particular disclosures in the specification, including the claims, as originally filed, which provide written support for the amendment to the specification.

Grounds of Objection and Rejection Withdrawn

7. Unless specifically reiterated below, the amendment or arguments filed August 5, 2004, have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed February 18, 2005.

Response to Arguments

8. At pages 36-40 of the amendment filed August 5, 2005, Applicant traversed the grounds of rejections of claims 12-19, 24, 26-28, 30, 32-40, 42-47, 51-62 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over US Patent Nos. 4,863,726 A or 4,894,227 A, and the grounds of rejections of claims 12-62 under 35 U.S.C. 103(a), as being unpatentable over US Patent Nos. 4,863,726-A or 4,894,227-A in view of Hank et al. (*Cancer Research* 1990; **50**: 5234-5239) and Keler et al. (*Cancer Research* 1997; **57**: 4008-4014), or Silwkowski et al. (*Seminars in Oncology* 1999; **26**: 60-70) and Lewis et al. (*Cancer Immunology & Immunotherapy* 1993; **37**: 255-263), and in further view of Meropol et al. (*Cancer Immunology & Immunotherapy* 1998; **46**: 318-326).

Although these grounds of rejection have been withdrawn, so as to state new grounds of rejection over the prior art, which are set forth below, Applicant's arguments are addressed to the extent those arguments might apply to a traversal of the new grounds of rejection.

Applicant argued that the rejection of claims 12-19, 24, 26-28, 30, 32-40, 42-47, 51-62 under 35 U.S.C. 102(b), as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over US Patent Nos. 4,863,726 A or 4,894,227 A, should be withdrawn because in order to establish a *prima facie* case of obviousness, the prior references must teach or suggest <u>all</u> the claim limitations, and it was Applicant's contention the prior art does not teach or fairly suggest the therapeutically effective dose of the anti-HER2 antibody or fragment thereof is in the range of from about 1.0 mg/kg to about 10.0 mg/kg and the therapeutically effective dose of the IL-2 polypeptide

or biologically active variant thereof is in the range of from about 0.5 MIU/m^2 to about 4.0 MIU/m^2.

In response, MPEP § 2143 states:

> Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." In re Kotzab, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). See also In re Lee, 277 F.3d 1338, 1342-44, 61 USPQ2d 1430, 1433-34 (Fed. Cir. 2002) (discussing the importance of relying on objective evidence and making specific factual findings with respect to the motivation to combine references); In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

The prior art teaches the combination of IL-2 or biologically active variants thereof, such as and in particular des-alanyl-1, serine-125 human IL-2 and an immunotoxin comprising the monoclonal antibody 520C9 for treating breast cancer. Although the prior art does not expressly teach the therapeutically effective dose of the anti-HER2 antibody or fragment thereof is in the range of from about 1.0 mg/kg to about 10.0 mg/kg and the therapeutically effective dose of the IL-2 polypeptide or biologically active variant thereof is in the range of from about 0.5 MIU/m^2 to about 4.0 MIU/m^2, the prior art does provide a working example and further discloses, "[t]he dosage and scheduling must be adjusted to obtain efficacious results" (column 25, lines 48 and 49).

At page 37 of the amendment filed August 5, 2005, Applicant discusses calculating the doses of antibody and IL-2 that would be administered to a human on the basis of the working example disclosed by the prior art. It appears, however, that Applicant's calculations are a *linear* extrapolation of the doses that were demonstrated to be effective in mice, where the starting doses of investigational anticancer drugs used in phase I clinical trials are not generally determined by such a method. For example, DeGeorge et al. (*Cancer Chemother. Pharmacol.* 1998; **41** (3): 173-185) teaches extrapolating such starting doses from preclinical animal toxicity studies, where traditionally that dose is one-tenth the dose lethal to 10% of rodents on a body surface area basis (milligrams per meter squared); see entire document, particularly page 176,

column 1. Furthermore, DeGeorge et al. explains that since studies that actually measure death as an endpoint are not required, so long as the dose range studied includes doses that cause severe, life-threatening toxicity, the starting dose is generally now chosen as one-tenth of the dose that causes severe toxicity (or death) in 10% of the rodents on a milligrams per square meter basis, provided this starting dose does not cause serious irreversible toxicity in a non-rodent species (page 176, paragraph bridging columns 1 and 2). Then, beginning at page 177, DeGeorge et al. describes the dose escalation scheme for phase I clinical trials, which often follows the standard or modified Fibonacci procedure (column 1). DeGeorge et al. discloses, "[a]lthough preclinical studies are used to determine the starting dose for phase I clinical trials, the highest doses for oncology drugs are rarely restricted by the doses used in preclinical toxicology studies as long as the toxicities of the new anticancer drug can be readily monitored, are reversible, and sufficiently precede lethality in animals" (page 177, column 1).

Thus, it is pertinent to point out that in phase I clinical trials of the use of Herceptin™ (trastuzumab) in combination with IL-2, Fleming et al. (*Clin. Cancer Res.* 2002 Dec; **8**: 3718-3727) teaches dose escalation of Herceptin™ from a starting dose of 1 mg/kg every two weeks to a dose of 8 mg/kg weekly; see entire document (e.g., the abstract). Notably, the starting dose of Herceptin™ that was used in this trial is equivalent to the lowest dose of the anti-HER2 antibody or fragment thereof to which the instant claims are directed, *and not merely half that dose*, which at page 37 of the amendment Applicant argued would be the highest dose administered following their linear extrapolation of the working example disclosed in the prior art. The "overview" of three open-label phase I trials, which began in 1992, to evaluate the safety and pharmacokinetics of trastuzumab, was not published until 1999[1]. Nevertheless, Baselga et al. (*J. Clin. Oncol.* 1996 Mar; **14** (3): 737-744) published the results of a phase II clinical trial studying the efficacy and toxicity of Herceptin™; see entire document. Baselga et al. teaches patients received an initial loading dose 250 mg

[1] Shak (*Semin. Oncol.* 1999 Aug; **26** (4 Suppl. 12): 71-77).

(abstract). If, as Applicant noted the average patient weighs 70 kg, this initial dose corresponds to a dose of about 3.6 mg/kg. Thus, this disclosure also indicates that contrary to Applicant's argument, the prior art would not have suggested administering to a human a dose of, at most, 0.5 mg/kg, because actual experience suggests otherwise, and the skilled artisan would not have performed a simple linear extrapolation of the data presented in the prior art to determine the starting dose to be used in human clinical trials.

Given the knowledge and skill in the art at the time the invention was made, as evidenced by, for example, the disclosures of DeGeorge et al. (*supra*) and Baselga et al. (*supra*), it is apparent that just as disclosed by U.S. Patent No. 4,863,726 A, the dosage and scheduling, which are adjusted to obtain efficacious results, will differ depending upon the type of cancer and the type of immunotoxin used, but are nonetheless "determined by routine experimentation" (column 25, lines 50-52).

Accordingly, contrary to Applicant's inference, the prior art should not be regarded as teaching away from the claimed invention, since, although the prior art does not expressly teach a dose of immunotoxin in the range of about 1 mg/kg to about 10.0 mg/kg, but instead teaches exemplary doses used in mice, which are not included in this range, it then teaches need to determine a safe and effective dose for use in humans. Furthermore, contrary to Applicant's arguments set forth at page 38, paragraph 2, of the amendment filed August 5, 2005, in view of the disclosures of DeGeorge et al. (*supra*) and Baselga et al. (*supra*), for example, it is believed that the dosing regimens, as recited in the instant claims, can be "simply extrapolated" from the working examples set forth in the prior art.

Then, with regard to the prior art's teaching of the appropriate dose of IL-2 that might be given a patient in a phase I clinical trial, contrary to Applicant's assertion at page 37, paragraph 2, of the amendment, it is submitted that the prior art would *not* suggest doses of IL-2 be administered to humans that are at least 31-fold higher than the highest dose in the low IL-2 dosing range, as claimed. As taught by DeGeorge et al. (*supra*), the starting dose is generally now chosen as one-tenth of the dose that causes severe toxicity (or death) in 10% of the rodents on a milligrams per square meter basis,

provided this starting dose does not cause serious irreversible toxicity in a non-rodent species. The prior art, however, does not teach the dose that caused severe toxicity (or death) in 10% of the mice. Notably, the prior art does teach the maximum tolerated dose (MTD) of *their IL-2 formulation* was found to be between 150-200 x 10^3 units, when given daily to immunocompetent mice for 14 days, but the prior art does not teach the MTD on a milligrams per square meter basis, and because the specific activity (i.e., the number of activity units per unit of mass, volume or molarity) of their IL-2 preparation is not disclosed, the MTD on a milligrams per square meter basis cannot be calculated (see, e.g., U.S. Patent No. 4,863,726 A; column 25, lines 36-39). Therefore, it is not possible for Applicant to make the comparison that they intended to make.

Nevertheless, here again, it is submitted that practical experience in the prior art would not have led the skilled artisan to have used doses of IL-2 in humans that are at least 31-fold higher than the highest dose in the low IL-2 dosing range, as claimed, despite any implication to have done so that might have been gathered from the disclosures of U.S. Patent Nos. 4,863,726 A and 4,894,227 A. For example, Kawase et al. (*Cancer Res.* 1988 Mar 1; **48**: 1173-1179), which discloses the combination of recombinant IL-2 and antitumor antibody capable of inducing antibody-dependent cellular cytotoxicity (ADCC), teaches administering 10 units of their IL-2 formulation having a specific activity of 3.5 x 10^4 units/mg to mice on a daily basis; see entire document, particularly page 1174, columns 1 and 2. The average weight of a mouse is 0.02 kg[2]. Accordingly, given the specific activity of their recombinant IL-2 formulation, Kawase et al. teaches administering 0.014 mg/kg daily. As Applicant has noted at the bottom of the second paragraph at page 37 of the amendment filed August 5, 2005, the present claims teach a dose *for mice* of 0.02-0.016 MIU. If this value were based upon the specific activity of Proleukin™, which is 18 x 10^6 international units (MIU)/1.1 mg[3], the claims are directed to an IL-2 dose for mice in the range of 0.006-0.05 mg/kg; and

[2] See, e.g., http://www.fda.gov/cder/cancer/animalframe.htm, which provides a dose calculator and indicates the average weight and corresponding estimated surface areas of different species of animal, including mouse and human.

accordingly, Kawase et al. teaches administering to mice a dose that falls within this range. As for practical experience in the prior art related to the treatment of humans with IL-2, Meropol et al. (*Clin. Cancer Res.* 1996 Apr; **2** (4): 669-677) (of record), for example, teaches the effectiveness of *low*-dose IL-2 to expand natural killer cells *in vivo* without significant toxicity; see entire document (e.g., abstract). Meropol et al. discloses treating patients with doses of Proleukin™ ranging from 0.4-1.75 MIU/m^2 daily, identifying 1.25 MIU/m^2 daily as the maximum tolerated dose (MTD); see, e.g., the abstract. Notably, the MTD taught by Meropol et al. falls within the range of the dose of recombinant IL-2 to which the claims are directed. Still other investigators consistently demonstrated the effectiveness of low-dose IL-2 treatment in patients afflicted with metastatic cancer to stimulate the expansion of natural killer cells. For example, Soiffer et al. (*Clin. Cancer Res.* 1996 Mar; **2** (3): 493-499) teaches effective "priming" doses of recombinant IL-2 as low as 0.45 x 10^6 units/m^2 daily followed by boluses of intermediate doses ranging from 0.25-1.0 x 10^6 units/m^2; see entire document (e.g., the abstract). Here, again, doses taught by the prior art fall within the range of the dose of recombinant IL-2 to which the claims are directed. So, contrary to Applicant's argument, it is submitted that the prior art would not have led the skilled artisan to administer such substantially larger doses of IL-2 in the practicing the claimed invention in the clinical setting.

Finally, although the prior art may not teach a dose of either the antibody (i.e., immunotoxin) or the variant of IL-2 that is precisely in the claimed range, it is nevertheless a common objective in the art to establish a dose that is both safe and effective, so as achieve optimal therapeutic effect and maximal benefit. See *In re Boesch*, 617 F.2d 272, 276, 205 USPQ 215, 219 (CCPA 1980) ("[D]iscovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." (citations omitted)). See *In re Peterson*, 65 USPQ2d 1379 1382 (CA FC 2003): "The normal desire of scientists or artisans to improve upon what is already

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[3] See, e.g., the PDR® entry for Proleukin™, PDR® Electronic Library™ (Copyright © 2002-2006 Thomson PDR); which is available on the Internet at http://www.micromedex.com/products/pdrlibrary/.

generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."

Regarding the rejections of claims 12-62 under 35 U.S.C. 103(a), as being unpatentable over US Patent Nos. 4,863,726-A or 4,894,227-A in view of Hank et al. (*Cancer Research* 1990; **50**: 5234-5239) and Keler et al. (*Cancer Research* 1997; **57**: 4008-4014), or Silwkowski et al. (*Seminars in Oncology* 1999; **26**: 60-70) and Lewis et al. (*Cancer Immunology & Immunotherapy* 1993; **37**: 255-263), and in further view of Meropol et al. (*Cancer Immunology & Immunotherapy* 1998; **46**: 318-326), Applicant argued the rejections should be withdrawn for a variety of reasons.

In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to Applicant's argument that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the Applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to Applicant's argument that there is no suggestion to combine the references, the Examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). As explained in responding to this same argument in the preceding Office action mailed February 18, 2005, such

motivation to have made the claimed invention is found in the in the references themselves.

Priority

9. Applicant's claim under 35 USC § 119(e) for benefit of the earlier filing date of the U.S. Provisional Application Serial No. 60/204,284, filed May 15, 2000, is acknowledged.

However, claims 12-73 do not properly benefit under 35 U.S.C. § 119(e) by the earlier filing dates of the priority documents claimed, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure.

To receive benefit of the earlier filing date under 35 USC § 119(e), the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Accordingly, the effective filing date of the claims is deemed the filing date of the instant application, namely May 14, 2001.

Grounds of Objection and Rejection Maintained

Claim Rejections - 35 USC § 112

10. The rejection of claims 12-73 under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for** using a method for treating a patient diagnosed with breast cancer that overexpresses HER2 comprising administering to the patient a therapeutically effective amount of Herceptin™ (trastuzumab) or an immunotoxin comprised of a humanized version of murine antibody 4D5, murine antibody 520C9, or another anti-HER2 antibody, as taught by the prior art, in combination with a

therapeutically effective amount of naturally occurring human IL-2, Proleukin™ (aldesleukin), or another recombinant human "IL-2" molecule effective to stimulate non-specific immune response in humans, as taught by the prior art, **does not reasonably provide enablement for** using a method for treating a subject having any cancer that is characterized by overexpression of HER2 according to the claims, is maintained. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

At pages 29-35 of the amendment filed August 5, 2005, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant has cited *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971) as an indication that the disclosure is presumed reasonably enabling for making and/or using the claimed invention in accordance with the requirement set forth under 35 U.S.C. §112, first paragraph, unless there is reason to doubt the objective truth to the statements and assertions contained therein. In response, the preceding Office action established a *prima facie* case supporting the Office's position that the disclosure would not be reasonably enabling of the claimed invention, as that position has been corroborated by factual evidence made of record that the skilled artisan could not make and/or use the claimed invention without undue and/or unreasonable experimentation.

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

Contrary to Applicant's assertions careful consideration of these factors in view of a preponderance of factual evidence of record indicates the claimed invention could not be used without undue and/or unreasonable experimentation.

Applicant has argued that the references cited by the Examiner do not in any way establish unpredictability. This argument is as unreasonable as it is unsubstantiated. The references cited in the preceding Office action (e.g., Stancovski et al; Lewis et al.) clearly indicate the skilled artisan cannot reliably and accurately predict which antibodies that binds the extracellular domain of HER2 ameliorate or aggravate disease symptoms in a subject afflicted with cancer, since it is not possible to predict which of such antibodies will inhibit or enhance the growth of cancer cells, and which will have no effect. Accordingly, the references indicate that merely knowing that a given antibody binds the extracellular domain of HER2 will not permit the skilled artisan to use the claimed invention to treat cancer in a subject, as it would first be necessary to determine *if* the antibody is effective to inhibit the growth of such cancer cells *in vivo*. Furthermore, the references cited in the preceding Office action clearly indicate that the skilled artisan cannot reliably and accurately predict which types of cancer characterized by the overexpression of HER2 can be treated using the claimed process, as it is not possible to predict which types of cancer overexpressing HER2 are "sensitive" to treatment with an anti-HER2 antibody that binds the extracellular domain of HER2. Accordingly, the

references indicate that merely knowing that a given cancer is characterized as overexpressing HER2 will not permit the skilled artisan to use the claimed invention to treat that cancer in a subject, as it would first be necessary to determine *if* the antibody is effective to inhibit the growth of such cancer cells *in vivo*. One cannot practice the claimed invention without undue and/or unreasonable experimentation if the disclosure would not permit the skilled artisan to know whether the claimed invention can be used effectively treat cancer in a subject. If one cannot practice the claimed invention without undue and/or unreasonable experimentation, the claims are not reasonably enabled by the disclosure.

Applicant's remarks regarding "IL-2 variants", which begin at page 30 of the amendment filed August 5, 2005, are acknowledged and have been carefully considered. As the claims are presently directed to an interleukin-2 polypeptide comprising SEQ ID NO: 1 or a biologically active variant thereof that comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 1 and activates NK cells, it is believed that the instant disclosure would enable the skilled artisan to make such polypeptides.

Beginning at page 33 of the amendment Applicant addresses the Office's position that the skilled artisan cannot reliably and accurately predict which anti-HER2 antibodies are therapeutically effective in the practice of the claimed invention. Applicant has argued that just because a determination must be made empirically does not mean undue experimentation is required. In response, inasmuch as determining whether any given antibody that binds the extracellular domain of HER2 inhibits the growth of cancer cells *in vitro* is largely a matter of routine using conventional methodology of which the artisan skilled in the relevant art is at least familiar, Applicant is correct that just because a determination must be made empirically does not mean undue experimentation is required. However, as Applicant has aptly noted in citing MPEP § 2164.08, which cites *In re* Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24, (CCPA 1970), "all that is necessary is that one skilled in the art be able to practice **the claimed invention**" (emphasis added). While it may be a matter of routine to screen anti-HER2 antibodies that bind the extracellular domain of HER2 to identify those that

are capable of inhibiting the growth of cancer cells characterized by the overexpression of HER2 *in vitro*, the claims are notably not drawn to such antibodies. Rather the claims are drawn to a method for treating such cancers in a subject by administering such antibodies in combination with IL-2 or a biologically active variant thereof. The references cited in the preceding Office action establish the fact that given the level of knowledge and skill in the art the disclosure would not be reasonably enabling of the claimed invention, as the skilled artisan could not make and/or use the claimed invention without first performing the undue and/or unreasonable experimentation that would be necessary to determine *if* the claimed invention can be used to achieve the claimed therapeutic effect. For example, given the knowledge and skill in the art, while the specification reasonably enables the use of a method for treating a patient diagnosed with breast cancer that overexpresses HER2, said method comprising administering to the patient a therapeutically effective amount of Herceptin™ (Trastuzumab) in combination with a therapeutically effective amount of Proleukin™ (Aldesleukin), the claims are directed to methods for treating any type of cancer characterized by the overexpression of HER2. Lewis et al. (of record), however, teaches that two types of cancer characterized by the overexpression of HER2, namely colon and gastric cancer, are not inhibited by treatment with monoclonal antibody 4D5. As Applicant has noted, MPEP § 2164.08, again citing In re Fisher (*Id.*), states, "the scope of enablement must only bear a 'reasonable correlation' to the scope of the claims" to satisfy the enablement provision set forth under 35 U.S.C. § 112, first paragraph. However, in this instance, given the disparity in the scope of enablement and the scope of the claims, it is submitted the former does not bear "reasonable correlation" to the latter.

Applicant has respectfully pointed out that it is the burden of the Examiner to show why one skilled in the art would consider the experimentation necessary to practice the claimed invention undue, as it is their contention, for example, that it would not be necessary to determine to which epitope an anti-HER2 antibody binds, only to determine if the antibody inhibits the growth of cancer cells. In response, as explained

in the preceding Office action, the specification has not provided the guidance and direction necessary to enable the skilled artisan to distinguish which anti-HER2 antibodies can or cannot be used effectively in the practice of the claimed invention. As evidenced by U.S. Patent No. 5,772,997 A (of record), for example, it appears only antibodies that bind a few particular epitopes of the extracellular domain of HER2 are capable of inhibiting the growth of tumor cells. Accordingly, U.S. Patent No. 5,772,997 A teaches the growth inhibitory properties of monoclonal antibody 4D5 are somewhat unique because other anti-HER2 antibodies were found to inhibit the growth of the cells to a lesser extent, or not at all; and notably others (Stancovski et al. (of record) and Lewis et al. (of record)) teach anti-HER2 antibodies binding the extracellular domain of HER2 that actually enhance, as opposed to inhibit the growth of cancer cells. Jiang et al. (*J. Biol. Chem.* 2005 Feb 11; **280** (6): 4656-4662) teaches that it is now well known that different biological effects are associated with epitope specificity of the antibodies; see entire document, particularly page 4656, column 2. Reimer et al. (*J. Immunol.* 2004; 173: 394-401) also teaches the diverse biological effects that are exerted by different anti-HER2 antibodies depends upon epitope specificity; see entire document (e.g., the abstract). Reimer et al. (*Mol. Immunol.* 2005; 42: 1121-1124) teaches, because antibodies binding the same antigens have been shown to both ameliorate and aggravate disease symptoms, the concept of epitope specificity, as opposed to mere antigen specificity, in humoral immunology has gained importance in modern medicine; see entire document, particularly page 1123, column 1.

Furthermore, the specification discloses only patients having breast cancer responded positively to treatment with exemplified embodiment of the invention. Again, Lewis et al. (of record) teaches monoclonal antibody 4D5 does not affect the proliferation of gastric and colon cancer cells, even though the cells express an amount of HER2 that is equivalent to the amount expressed by breast cancer cells that are sensitive to the effects of treatment with the antibody. Given this fact, it would appear that the skilled artisan could not use the claimed invention to treat gastric and colon cancers in subjects; and otherwise, apart from breast cancers overexpressing HER2, the skilled artisan could not use the claimed invention without first determining whether

other types of cancer are inhibited by treatment with a suitable anti-HER2 antibody that binds the extracellular domain of HER2. As evidenced by Lewis et al., for example, the skilled artisan cannot accurately and reliably predict which types of cancer can or cannot be treated using the claimed invention simply upon the basis of the level of expression of HER2. As such, for each and every type of cancer characterized as overexpressing HER2, other than such breast cancers, undue and/or unreasonable experimentation would have to be performed so as to determine *if* the claimed invention can be used to treat that type of cancer.

The concept of treating cancer by coadministering IL-2 and an antitumor monoclonal antibody capable of inducing antibody-dependent cellular cytotoxicity is not new; for example, as early as 1988 investigators, such as Kawase et al. (*Cancer Res.* 1988 Mar 1; **48** (5): 1173-1179) were using such combined therapy to treat lymphokine-activated killer-resistant tumors in mice; see entire document (e.g., the abstract). As explained in the preceding Office action, it appears from Applicant's disclosure that any greater effectiveness of the combination, per se, of Herceptin™ (i.e., Trastuzumab, a recombinant humanized version of murine monoclonal antibody 4D5) and Proleukin™ (i.e., Aldesleukin, a recombinant human IL-2 mutein), as compared to that of the monotherapeutic use of the antibody, would depend upon the ability of the antibody to mediate antibody-dependent cell cytotoxicity (ADCC). If not, the presence of IL-2-activated effector cells would not be expected to enhance the antiproliferative, i.e., therapeutic, effect of an anti-HER2 antibody. However, the claims are not limited to any such proven combination, but are instead directed to a combination of any member of a genus of anti-HER2 antibodies that bind the extracellular domain of HER2 and an IL-2 polypeptide capable of activating natural killer (NK) cells. Applicant has dismissed this issue citing seemingly irrelevant case law, which Applicant argues indicates the enablement requirement is met if the description enables any mode of making and using the claimed invention. If, by that line of reasoning, Applicant is alleging that it is not necessary that the disclosure reasonably enable the breadth of the claimed invention, there is ample case law to refute such a position. Nevertheless, as previously

explained, the recombinant humanized version of the murine monoclonal antibody 4D5, namely Herceptin™ has been shown to mediate ADCC; and the conventional wisdom in the art is that it is by this mechanism, albeit not by this mechanism alone, that Herceptin™ mediates its growth inhibitory effects upon tumors in patients. However, Lewis et al. (of record) teaches that the *murine* monoclonal antibody does not mediate ADCC, and is further incapable of fixing complement to mediate complement-mediated cell cytotoxicity. Thus, if by no other mechanism Herceptin™ achieves its effectiveness, the teachings of Lewis et al. suggest that because the murine antibody does not mediate ADCC, a murine anti-HER2 antibody that binds the extracellular domain of HER2 cannot be used in practicing the claimed invention with effect before first determining whether the antibody effectively inhibits the growth of cancer cells in patients by some other mechanism and whether administering IL-2 in combination with the antibody will enhance or perturb this mechanism. Stancovski et al. (of record) teaches none of the disclosed anti-HER2 antibodies, which inhibited the growth of tumor cells, mediated ADCC, which suggests the mechanism by which mouse anti-HER2 antibodies typically affect the proliferation of cells is not effector cell (e.g., NK cell)-dependent, and further suggests that monoclonal antibody 520C9, as a murine antibody, is unusual in its ability to mediate ADCC. Given the teachings of Lewis et al. and Stancovski et al., it is submitted that murine anti-HER2 antibodies, including mouse monoclonal antibody 4D5, should not generally be regarded as suitable for use in the practice of the claimed invention, since most murine antibodies lack the ability to mediate ADCC in humans and are therefore not therapeutically equivalent to Herceptin™. Furthermore, even though monoclonal antibody 520C9 is capable of mediating ADCC, an embodiment of the claimed invention in which the monoclonal antibody is used has not been exemplified. The art teaches that a bispecific recombinant antibody comprising an antigen-binding fragment of monoclonal antibody 520C9 inhibited the growth of tumor cells; and the art also teaches that an immunotoxin comprising the antibody can be used to inhibit the growth of tumor cells. However, the art does not teach that monoclonal antibody 520C9 itself, or any fragment thereof, is

capable of effectively inhibiting the growth of tumor cells *in vivo*. To the contrary, Keler et al. (of record) teaches the $F(ab')_2$ fragment of monoclonal antibody 520C9 is relatively incapable of mediating ADCC, as compared to MDX-H210, a recombinant bispecific antibody comprising a Fab' fragment of 520C9.

It has long been known that the ability of an antitumor antibody to induce antibody-dependent cellular cytotoxicity (ADCC) and complement-mediated cytotoxicity is at least partially dependent upon the antibody's isotype. For example, Masui et al. (*Cancer Res.* 1986 Nov; **46** (11): 5592-5598) teaches anti-EGFR antibodies mediate antitumor effects by different mechanisms, which are at least partially determined by the different isotypes of these antibodies; see entire document (e.g., the abstract). More recently, Kim et al. (*Int. J. Cancer.* 2002; 102: 428-434) determined using anti-HER2 antibodies that both isotype *and epitope specificity* are important determinants of the antitumor effect of the antibodies; see entire document (e.g., the abstract). Kim et al. teaches antibodies of two epitope binding specificities, which are of different isotypes (abstract). Kim et al. teaches none of the antibodies specific for one epitope suppressed the growth of cancer cells *in vivo*; see, e.g., page 433, column 1 and Figure 7. Kim et al. teaches one of these antibodies that was ineffective *in vivo* had demonstrated considerable antitumor activity *in vitro*, as measured using ADCC and complement-dependent cytotoxicity (CDC) assays; see, e.g., page 433, column 1. Kim et al. teaches each of the antibodies specific for the other epitope showed antitumor activities *in vivo* (page 433, column 1). The antibody of IgG2b isotype exhibited the strongest antitumor activity in vivo; and the antibody of IgG1 isotype showed a moderate level of antitumor activity, whereas the antibody of IgG2a isotype was only slightly effective (page 433, column 1). Kim et al. discloses, "[i]t was surprising that HRT G2b [i.e., the antibody of IgG2b isotype] was most effective among the HRT isotype antibodies *in vivo*, whereas the HRT G2a [i.e., the antibody of IgG2a isotype] showed only a slight effect" (page 433, column 1). Kim et al. therefore concludes the results of the *in vivo* studies could not be explained by the results obtained from the *in vitro* studies, which suggests the antitumor effects of these antibodies might involve still other mechanisms not yet identified or understood. Nevertheless, Kim et al. teaches

their results clearly indicate that the epitope specificity of antitumor antibodies, in addition to their isotypes, determines their ability to exert effective antitumor activity both *in vitro* and *in vivo* (page 433, column 1). Given the complexity and unpredictability made evident by the teachings of Kim et al., it is submitted that the skilled artisan could not practice of the claimed invention without undue and/or unreasonable experimentation. As previously explained, it is not sufficient to merely know that an antibody binds the extracellular domain of HER2, as it cannot be predicted whether the antibody will be effective to inhibit cancer cells. Moreover, in light of Kim et al., it is also not sufficient to merely know that an antibody that binds the extracellular domain of HER2 is capable of mediating ADCC or CDC *in vitro*, as it cannot be predicted whether the antibody will be effective *in vivo*. Kim et al. also underscores the conclusions that have been made on the basis of the teachings of Stancovski et al. and Lewis et al.; Kim et al. also teaches the epitope specificity is an important determinant of the antitumor activity of an anti-HER2 antibody.

Further demonstrating the complexity, as well as the unpredictability in this area of the art, Vuist et al. (*Cancer Res.* 1990 Sep 15; **50** (18): 5767-5772) teaches treatment of cancer cells with an antitumor antibody of the isotype IgG2a was therapeutically active by itself, but IgG1 and IgG2b isotype variants of this antitumor antibody were not; see entire document (e.g., the abstract). Although both IgG1 and IgG2b isotype variants were ineffective alone, Vuist et al. teaches their combination with recombinant IL-2 resulted in significant antitumor effects (abstract). The antibody of IgG2a isotype, which was effective alone, was more so in combination with recombinant IL-2 (abstract). Vuist et al. discloses further characterization of these antibodies using *in vitro* studies suggests the isotypes that were ineffective alone (i.e., IgG1 and IgG2b) mediated IL-2-induced antibody-dependent cellular cytotoxic activity of lymphocytes in the presence of IL-2. Vuist et al. speculates that in the presence of IL-2 the antitumor activity of the antibody of IgG2a isotype may involve both IL-2-induced antibody-dependent cellular cytotoxic activity of lymphocytes and IgG2a-restricted antitumor activity of monocytes/macrophages (abstract). Thus, contrasting other disclosures, such as Kim et al. (*supra*), Vuist et al. provides factual evidence that mere knowledge of the isotype

of an antitumor antibody does not provide a fair indication that the antibody in combination with IL-2 will be capable of mediating ADCC *in vivo*, so as to be therapeutically effective and useful in the practice of the claimed invention. Furthermore, the teachings of Vuist et al. suggest mere identification of anti-HER2 antibodies capable of inhibiting the growth of cancer cells will not provide reliable indication that the antibody can or cannot be used in combination with IL-2 to treat cancer *in vivo*, since Vuist et al. discloses effective treatment of cancer cells with antibodies, which were not effective alone, in the presence of IL-2.

As a new matter, with particular regard to claim 26, which is directed to the process of claim 12, wherein said dose of IL-2 or variant thereof is administered as a pharmaceutical composition selected from a group that includes a "lyophilized" composition and a "spray-dried" composition, the prior art does not appear to teach administering such compositions. Instead, the prior art teaches reconstituting such "dry" compositions in a pharmaceutically acceptable carrier for administration to the patient. The specification appears to be deficient therefore in teaching how such "dry" compositions are administered.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), there appears a preponderance of factual evidence of record indicating the amount of guidance, direction, and exemplification disclosed in the specification, as filed, would be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

11. The rejection of claims 25, 31, 52, 55, 58, 61, and 63-73 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

At pages 35 and 36 of the amendment filed August 5, 2005, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

As explained in the preceding Office action, provided one has assess to the hybridoma producing said antibodies, MPEP § 2401.01 states to avoid the need for a deposit, biological materials must be known and readily available – *neither concept alone suffices*.

Applicant has provided Appendix A, which is a list of publications identified as disclosing antibodies designated 4D5 and/or 520C9. Even given the presumption that these disclosures refer the same antibodies to which the claims are directed, again, the fact that Applicant and other members of the public were able to obtain the materials in question from a given depository or that reference to the material or a deposit thereof has been made in various publications prior to and after the filing date of the application does not establish that upon issuance of a patent on this application that such material would continue to be accessible to the public.

Applicant's have remarked that U.S. Patent Nos. 5,677,171 and 6,054,561 refer to deposits under ATCC Accession Nos. CRL 10463 and HB8696, respectively, of the hybridoma cell lines, which allegedly produce the antibodies to which the claims refer. However, as explained in the preceding Office action, the applications (i.e., 08/286,303 and 08/483,749) upon which these patents issued cannot be attained for review of the record, as the applications are presently located with the Board of Patent Appeals and Interferences. The applications must be reviewed to determine whether the record includes a statement by an attorney of record having authority and control over the conditions of the stated deposit that the deposit had been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits were to be irrevocably removed upon the grant of a patent on the application, and that the deposit would be replaced if viable samples cannot be dispensed by the depository and whether there was a provision of assurances that all restrictions imposed by the depositor on the availability to the public

of the deposited material were to be irrevocably removed upon the granting of the patent. Applicant has not provided the required assurance that said depository would allow unlimited access to the material upon the issue of a patent upon this application.

In further response to the preceding Office action, Applicant has provided Appendix B, which includes copies of pages of the ATCC catalog, which is viewable on the Internet at http://www.atcc.org/. The pages of this catalog indicate that hybridoma cell lines designated "A-HER2 [4D5; NB9644P28]" and ""520C9 [520C9.C3B10T]" bearing ATCC accession numbers CRL-10463™ and HB-8696™, respectively, are commercially available with the provision that the terms and conditions of ATCC's Material Transfer Agreement or, in certain cases, an MTA specified by the depositing institution be read and accepted. In addition, the catalog indicates that the materials are cited in a U.S. and/or other Patent or Patent Applications, and may not be used to infringe on the patent claims.

Applicant has not made of record any of the facts and circumstances surrounding the access to the biological materials from said depository, which are dictated by the terms and conditions of ATCC's Material Transfer Agreement or, in certain cases, an MTA specified by the depositing institution.

Moreover, Applicant has not established a nexus between these deposited materials and the antibodies to which the claims specifically refer.

Again, as explained in the preceding Office action, if Applicant can establish that hybridomas producing monoclonal antibodies 4D5 and 520C9 are known and readily available, the Office will accept the showing. However, establishing that these antibodies to which the claims refer are both known and readily available requires Applicant to provide a showing that antibodies, which are known and readily available, are, in fact, the *same* antibodies to which the claims are directed. Such a showing provides a nexus "tying" together the antibodies to which the claims are directed and the antibodies allegedly known and readily available. Until such a nexus is identified in the specification, including the claims, as originally filed, in the absence of evidence that the hybridoma producing monoclonal antibodies 4D5 and 520C9 are readily available to the public and that all restrictions imposed by the depositor, or by other investigators on the

availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, the rejection is properly maintained.

Finally, Applicant has provided Appendix C, which are pages printed from the Internet describing Herceptin™; however, as none of the claims are specifically directed to Herceptin™, the issue of the readiness of public access is not presently at issue.

Having not resolved this issue, Applicant is again advised that a suitable deposit would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph (see 37 C.F.R. 1.801-1.809), provided the specification, as originally filed, provides a nexus to hybridomas producing same antibodies to which the claims are directed. See MPEP § 2406.01.

If a deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit has not been made under the Budapest treaty, then an affidavit or declaration by Applicant or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature must be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth under 37 CFR §§ 1.801-1.809 have been met.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except

if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

New Ground of Objection

Specification

12. The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

An example of such improperly demarcated trademarks is Proleukin™ (page 29, lines 3).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

13. Claims 28-31, 71, and 72 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 28-31 are indefinite because claim 28 recites, "said variant of human IL-2". There is no antecedent basis in any of preceding claims 12, 26, and 27. Consequently the metes and bounds of the subject matter that is regarded as the invention cannot be determined, so as to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

Claim 71 is indefinite because the claim recites, "said introductory cycle". There is no antecedent basis in preceding claim 63. Consequently the metes and bounds of the subject matter that is regarded as the invention cannot be determined, so as to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

Claim 72 is indefinite because the claim recites, "said subsequent cycle". There is no antecedent basis in preceding claim 63. Consequently the metes and bounds of the subject matter that is regarded as the invention cannot be determined, so as to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

14. Claims 12-73 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained.

This is a "new matter" rejection.

(a) Claims 12, 16, 17, 42, and 63 recite, "an interleukin-2 (IL-2) polypeptide comprising SEQ ID NO: 1".

This limitation finds support in the specification at page 29 in the paragraph beginning in line 2, as amended August 5, 2005, which reads: "The IL-2 in this formulation [i.e., Proleukin™] is a recombinantly produced human IL-2 mutein, called aldesleukin (SEQ ID NO:1), which differs from the native human IL-2 sequence in having the initial alanine residue eliminated and the cysteine residue at position 125 replaced by serine (referred to as des-alanyl-1, serine-125 human interleukin-2)".

At page 21, paragraph 2, of the amendment filed August 5, 2005, Applicant has asserted that the specification, as originally filed, provides support for amending the specification at page 29 in the paragraph beginning in line 2 to provide antecedent basis for this claim language, since "[t]his sequence (i.e., SEQ ID NO: 1) is disclosed in Fig. 15b of U.S. Patent No. 4,518,584, which patent was incorporated by reference in the present specification, for example, at page 17, line 21". The disclosure at page 17 (lines 19-21) referring to U.S. Patent No. 4,518,584 reads, "the recombinant IL-2 muteins described in European Patent Application No. 83306221.9, filed Oct. 13, 1983

(published May 30, 1984 under No. 109748), which is the equivalent to Belgian Patent No. 893,016; U.S. Patent No. 4,518,584". This disclosure, however, does not appear to provide a nexus between the amino acid sequence set forth as the amino acid sequence depicted in Figure 15b of U.S. Patent No. 4,518,584 (i.e., SEQ ID NO: 1) and aldesleukin (i.e., des-alanyl-1, serine-125 human interleukin-2, or Proleukin™).

Thus, while the inclusion of SEQ ID NO: 1 in the claims finds support in the specification, as amended August 5, 2005, the original disclosure provides no apparent nexus between the amino acid sequence set forth as SEQ ID NO: 1 and aldesleukin (i.e., des-alanyl-1, serine-125 human interleukin-2, or Proleukin™), which might serve as a basis for the amendment to the specification. If the amendment to the specification finds no written support in the specification, including the claims, as originally filed, then amending the claims to recite "SEQ ID NO: 1" introduces new matter and thereby violates the written description requirement set forth under 35 U.S.C. § 112, first paragraph.

This issue might be resolved if Applicant were to point to particular disclosures in the specification, including the claims, as originally filed, which are believed to provide written support for the amendment to the specification and thus to the language of the claims, namely a nexus between the sequence depicted in Figure 15b of U.S. Patent No. 4,518,584, which has been incorporated by a reference to the patent at page 17 of the originally filed specification, and the primary structure (i.e., amino acid sequence) of Proleukin™ (aldesleukin).

Note: Claims 28-31 are indefinite for the reason set forth above in the rejection of those claims under 35 U.S.C. § 112, second paragraph. If claim 28 were amended to properly limit preceding claims 12, 26, and 27, such that the claim is directed to a process comprising administering "des-alanyl-1, serine-125 human interleukin-2", as opposed to "an interleukin-2 (IL-2) polypeptide comprising the sequence of SEQ ID NO:1 or a biologically active variant thereof", claims 28-31 would not be rejected as failing to meet the written description requirement for recitation of new matter. "Des-alanyl-1, serine-125 human interleukin-2" is described in the specification, for example,

at page 29 as the recombinantly produced human IL-2 mutein, which is also designated aldesleukin and manufactured by Chiron Corporation under the tradename Proleukin™.

(b) Claims 12, 16, 17, and 42 recite "an interleukin-2 (IL-2) polypeptide comprising the sequence of SEQ ID NO:1 or a biologically active variant thereof [...] wherein said variant of IL-2 activates NK cells and comprises an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 1". Accordingly, claims 12-62 are directed to a genus of variants of a polypeptide comprising the amino acid sequence of SEQ ID NO: 1, which comprise amino acid sequences that are at least 90% identical to SEQ ID NO: 1.

Applicant has asserted that support for the amendment of claims drawn to this genus is found throughout the specification, including, for example, at page 14, lines 11-14.

The disclosure at page 14, lines 11-14, to which Applicant has specifically referred teaches, "biologically active variants of IL-2 will generally have at least 70%, preferably at least 80%, more preferably about 90% to 95% or more, and most preferably about 98% or more amino acid sequence identity to the amino acid sequence *of the reference polypeptide molecule, which serves as the basis for comparison*" (italicized for added emphasis).

Thus, this disclosure describes biologically active variants of "IL-2", which generally have at least 90% amino acid sequence identity to the amino acid sequence of the reference polypeptide, which serves as the basis of comparison. The term "IL-2" is explicitly defined in the specification at page 12, lines 8 and 9, to mean: "A lymphokine that is produced by normal peripheral blood lymphocytes and is present in the body at low concentrations". At page 12, lines 9-14, the specification further describes "IL-2" as first described by Morgan et al. (1976) and originally called T cell growth factor because of its ability to induce proliferation of stimulated T lymphocytes, and is a protein with a reported molecular weight in the range of 13,000 to 17,000 (Gillis and Watson (1980)) and has an isoelectric point in the range of 6-8.5.

However, the particular disclosure at page 14 to which Applicant has referred does not provide written support for variants of a polypeptide comprising the amino acid

sequence of SEQ ID NO: 1, per se, nor does it provide written support for variants of such a polypeptide comprising amino acid sequences that are at least 90% identical to amino acid sequence of that polypeptide (i.e., SEQ ID NO: 1). Moreover, it appears that the specification only provides written support for suitable biologically active variants of native and naturally occurring IL-2, including "fragments", analogues", and "muteins", as opposed to *variants of such variants*; see, in particular, page 13, lines 6 and 7.

This issue might be resolved if Applicant were to point to particular disclosures in the specification, including the claims, as originally filed, which are believed to provide written support for the language of the claims.

(c) Claims 12, 16, 17, and 42 recite "an interleukin-2 (IL-2) polypeptide comprising the sequence of SEQ ID NO:1 or a biologically active variant thereof [...] wherein said variant of IL-2 activates NK cells". Accordingly, claims 12-62 are directed to a genus of variants of a polypeptide comprising the amino acid sequence of SEQ ID NO: 1, which comprise amino acid sequences that are at least 90% identical to SEQ ID NO: 1 and have the shared ability to activate natural killer (NK) cells.

Applicant has asserted that support for the amendment of claims drawn to this genus is found throughout the specification, including, for example, at page 12, lines 20 and 21; page 27, lines 7-14; page 32, lines 13 and 14; and page 34, lines 9-17.

The disclosure at page 12, lines 20 and 21, teaches, "pharmaceutical compositions useful in the methods of the invention may comprise biologically active variants of IL-2".

The disclosure at page 27, lines 7-14, teaches, "functional consequences of IL-2 binding on NK cells is dependent upon the specific receptor complexes present" and "[a]ctivation of the high affinity heterotrimeric receptor with picomolar concentrations of IL-2 provides a proliferative stimulus, without augmenting cytotoxicity [whereas] nanomolar concentrations of IL-2 that bind the intermediate-affinity beta-gamma IL-2 receptor complex result in augmented effector cell cytotoxicity, with little effect on proliferation".

The disclosure at page 32, lines 13 and 14, teaches, "[l]ow-dose IL-2 was administered to expand the NK cell population *in vivo* and was given on an outpatient basis and patient self-administration was encouraged".

The disclosure at page 34, lines 9-17, teaches cytotoxicity assays were performed and cytotoxicity was measured both with and without patient serum containing anti-HER2 monoclonal present at the time of phlebotomy.

None of the disclosures to which Applicant has specifically referred appear to provide written support for the claimed invention, as none appear to adequately describe a genus of variants of a polypeptide comprising the amino acid sequence of SEQ ID NO: 1, which have the shared ability to activate natural killer (NK) cells, per se. Moreover, none of the disclosures to which Applicant has specifically referred appear provide proper and sufficient written description of a genus of variants of a polypeptide comprising the amino acid sequence of SEQ ID NO: 1 having an amino acid sequence that is at least 90% identical to SEQ ID NO: 1, which have the shared ability to activate natural killer (NK) cells. Rather the specification, as originally filed, appears to only provide written support for a genus of variants of native and naturally occurring "IL-2" having an amino acid sequence that is at least 90% identical to the amino acid sequence said "IL-2", which "retain the desired biological activity of the native polypeptide such that the pharmaceutical composition comprising the variant polypeptide has the same therapeutic effect as the pharmaceutical composition comprising the native polypeptide when administered to a subject" (page 12, lines 21-24; also see, e.g., page 13, lines 6 and 7; and page 14, lines 11-21. A variant of native "IL-2" is not equivalent to a variant of a polypeptide comprising SEQ ID NO: 1, since a polypeptide comprising SEQ ID NO: 1 is itself a variant of a native human IL-2; see, e.g., page 29, lines 2-7. Moreover, while the members of the genus of variants to which the claims are directed might be said to "retain the desired biological activity of the native polypeptide such that the pharmaceutical composition comprising the variant polypeptide has the same therapeutic effect as the pharmaceutical composition comprising the native polypeptide when administered to a subject", the specification, as

originally filed, does not appear to describe such a genus of variants that activate NK cells, per se.

This issue might be resolved if Applicant were to point to particular disclosures in the specification, including the claims, as originally filed, which are believed to provide written support for the language of the claims.

15. Claims 12-73 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105).

In this instance, the claims are directed to methods for treating cancer comprising administering to a subject having cancer a member of a genus of anti-HER2 antibodies or fragments thereof that bind to the extracellular domain HER2. *Ipsis verbis* support for "an anti-HER2 antibody or fragment thereof" is found throughout the specification, including the claims, as originally filed; and at page 21, lines 23-25, for example, the specification describes such antibodies as preferably binding the extracellular portion of HER2. Even so, the Federal Circuit has explained that *ipsis verbis* support for the

claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

To achieve the claimed therapeutic effect, the genus of anti-HER2 antibodies to which the claims are directed, which bind specifically to the extracellular domain of HER2, must be effective to inhibit the growth of cancer cells *in vivo*. Were the instant disclosure adequate to reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed, the disclosure would also necessarily permit the skilled artisan to immediately envision, recognize or distinguish at least a substantial number of the members of this genus of therapeutically effective antibodies that are useful in practicing the invention to achieve the claimed therapeutic effect.

"[G]eneralized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004). In this instance, there is no language that adequately describes the genus of anti-HER2 antibodies binding the extracellular domain of HER2, which when *not* conjugated to a cytotoxic moiety, inhibit the growth of cancer cells, so as to provide therapeutic benefit in treating cancer in a subject using the claimed invention. A description of what a material does, rather than of what it is, does not suffice to describe the claimed invention.

Notably the Federal Circuit has recently decided that the description of a fully characterized molecular target of an antibody is sufficient to adequately describe an antibody that binds that target. See *Noelle v. Lederman*, 69 USPQ2d 1508 (CA FC

2004). However, the same court decided that each case involving the issue of written description, "must be decided on its own facts. Thus, the precedential value of cases in this area is extremely limited." *Vas-Cath*, 935 F.2d at 1562 (quoting *In re Driscoll*, 562 F.2d 1245, 1250 (C.C.P.A. 1977)).

Following the example set by the Federal Circuit in deciding *Noelle v. Lederman*, then, were the claims directed to an antibody that binds a well-characterized antigen, the written description would be met. However, the claims are not solely directed to an antibody that binds a well-characterized molecular target; rather the claims are directed to a genus of naked antibodies (i.e., antibodies not conjugated to cytotoxins) that bind the extracellular domain of HER2 and inhibit the growth of cancer cells *in vivo*, so as to be therapeutically effective in treating cancer in a subject.

The specification describes murine monoclonal antibody 4D5; however, as explained in the preceding Office action at page 13, for example, the naked, unconjugated antibody does not inhibit the growth of every type of cancer cell characterized by the overexpression of HER2. For example, Lewis et al. (of record) teaches murine monoclonal antibody 4D5 did not inhibit the growth of colon or gastric cancer cells, despite their overexpression of HER2. Furthermore, as explained at page 14 of the preceding Office action, naked murine monoclonal antibody 4D5 does not mediate antibody-mediated cell cytotoxicity (ADCC), nor does it mediate complement-mediated cell cytotoxicity. Only the recombinant humanized version of the murine antibody (i.e., Herceptin™ (Trastuzumab)) has been shown to mediate ADCC.

The specification also describes murine monoclonal antibody 520C9. As explained in the preceding Office action, while the naked antibody mediates ADCC, its ability to do so appears relatively unique and its use *in vivo* to achieve therapeutic benefit in treating cancer that overexpresses HER2 has not apparently been reported; see, e.g., pages 14 and 15 of the preceding Office action. While immunoconjugates comprising murine monoclonal antibody 520C9, a fragment thereof, or a recombinant version thereof and toxins (e.g., ricin) or other "effector" moieties (e.g., MDX-210[4]) have

[4] Repp et al. (*J. Hematother.* 1995 Oct; **4** (5): 415-421).

been shown to be effective *in vivo*, few naked antibodies have apparently been reported to achieve clinically or therapeutically significant benefits in treating cancer. Absent conjugation to a cytotoxic moiety, the best characterized anti-HER2 antibodies shown to be effective to inhibit the growth of cancer cells *in vivo* are those commonly binding the particular epitope to which murine monoclonal antibody 4D5 (e.g., Herceptin™) binds. Again, naked, unconjugated murine monoclonal antibody 520C9 has not apparently been reported to achieve such benefits.

Accordingly, apart from Herceptin™, it appears the specification fails to describe an antibody that is *not* conjugated to a toxin moiety (e.g., a radionuclide or chemotherapeutic agent), which inhibits the growth of cancer cells *in vivo*. Inasmuch as the clinical effectiveness of Herceptin™ (i.e., a naked recombinant humanized version of murine monoclonal antibody 4D5) appears *unique*, it is noteworthy that the specification fails to describe the genus of antibodies to which the claims are directed as binding specifically to the same "epitope" of HER2 as monoclonal antibody 4D5 and Herceptin™. Moreover, the specification does not describe the one, or possibly more "epitopes" to which the genus of antibodies must bind, if not conjugated to a cytotoxic moiety, so as to yield the claimed therapeutic effect *in vivo* during the practice of the claimed invention.

There is factual evidence that the detailed description of an antigen, as opposed to the detailed description of *an epitope* of an antigen, should not always be regarded as sufficient to describe the antibody that binds that antigen, particularly in instances where binding of the antibody modulates the activity of the antigen and/or effects the growth of cells expressing the antigen. For example, Stancovski et al. (of record) characterized the binding effects upon the growth of tumor cells of different antibodies, each of which bind different epitopes of the extracellular domain of a tumor-associated antigen related to EGFR, namely ErbB2; see entire document (e.g., the abstract). Stancovski et al. teaches some anti-ErbB2 antibodies inhibited tumor cell growth, but others actually accelerated their growth (page 8693, column 1). By way of explanation, Jiang et al. (*J. Biol. Chem.* 2005 Feb 11; **280** (6): 4656-4662) teaches that it is well known that different biological effects are associated with epitope specificity of the

antibodies; see entire document, particularly page 4656, column 2. Reimer et al. (*J. Immunol.* 2004; 173: 394-401) also teaches the diverse biological effects that are exerted by different anti-HER2 antibodies depends upon epitope specificity; see entire document (e.g., the abstract). Reimer et al. (*Mol. Immunol.* 2005; 42: 1121-1124) teaches, because antibodies binding the same antigens have been shown to both ameliorate and aggravate disease symptoms, the concept of epitope specificity, as opposed to mere antigen specificity, in humoral immunology has gained importance in modern medicine; see entire document, particularly page 1123, column 1.

Accordingly, the mere generalized description of antibodies that bind a well-characterized antigen, as opposed to a well-characterized *epitope* of an antigen, cannot always suffice to describe adequately antibodies that have, for example, an inhibitory or therapeutic effect, because the skilled artisan could not immediately envision, recognize, or distinguish those antibodies that bind an antigen on tumor cells and inhibit the growth of those tumor cells from antibodies that bind the antigen but lack therapeutic effect (e.g., promote the growth of tumor cells).

Although the specification teaches two anti-HER2 antibodies that are used allegedly useful in practicing the claimed invention to achieve the clinical or therapeutic benefit in a subject afflicted with cancer, unless conjugated to a cytotoxic moiety (e.g., a biological toxin, such as ricin, or a radioisotope), only monoclonal antibody 4D5 and recombinant derivatives thereof that retain the epitope binding specificity of the "parent" antibody have well-established efficacy in treating breast cancers characterized by relatively high overexpression of HER2. The other monoclonal antibody, namely 520C9, which binds the extracellular domain of HER2, has apparently also not been shown to effectively inhibit the growth of cancer cells *in vivo*, unless it is conjugated to a cytotoxic moiety. Given the different epitope specificity of these two antibodies and others described in the relevant literature, which have different effects upon the growth of cancer cells expressing HER2, it is apparent that neither antibody should be regarded as representative of the genus, as a whole, of anti-HER2 antibodies that bind specifically to the extracellular domain of HER2, which are effective to inhibit the growth of cancer cells characterized as overexpressing HER2 in practicing the claimed

invention. Moreover, because these many antibodies commonly bind to the extracellular portion of HER2, the simple description of the antigen, as opposed to the epitope of the antigen, to which the antibodies bind does not apparently suffice to adequately describe the genus of therapeutically useful anti-HER2 antibodies that are effective to inhibit the growth of cancer cells in the practice of the claimed invention, because the skilled artisan cannot immediately envision, recognize, or distinguish such therapeutically effective antibodies from other antibodies that bind the extracellular domain of HER2.

It is aptly noted that the Federal Circuit has decided that a generic statement that defines a genus of substances by *only* their functional activity, i.e., the ability to specifically bind a polypeptide and inhibit its activity, or the ability to bind a cancer cell and inhibit its growth or metastatic progression, does not provide an adequate written description of the genus. See *The Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997). The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

Although *Lilly* related to claims drawn to genetic material, the statute applies to all types of inventions. "Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1984 (CAFC 2004). Without at least a substantial number of the members of the genus of anti-HER2 antibodies that bind the extracellular domain of HER2 and inhibit its

activity, so as to be therapeutically effective without the necessity of conjugating the antibody to a cytotoxic moiety, it is impossible to use the claimed invention.

Although the skilled artisan could potentially screen candidate anti-HER2 antibodies to identify those that bind HER2 and inhibit its function, so as to be therapeutically effective in treating cancer, it is duly noted that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Claim Rejections - 35 USC § 102

16. Claims 12-15, 17, 22-26, 35-37, 51, 52, 57, 58, 63, 64, 66, 68, and 73 are rejected under 35 U.S.C. 102(b) as being anticipated by Fleming et al. (Abstract No. 710, Program Proceedings, American Society of Clinical Oncology, 35th Annual Meeting, 1999) (of record), as evidenced by Fleming et al. (*Clin. Cancer Res.* 2002 Dec; **8**: 3718-3727).

Fleming et al. teaches administering to patients a recombinant anti-HER2 monoclonal antibody in combination with IL-2. Fleming et al. teaches the antibody, as a single agent, has already been demonstrated to be therapeutically effective in treating patients afflicted with breast cancer characterized by the overexpression of HER2, and IL-2 activates natural killer cells *in vivo*. Fleming et al. teaches IL-2 doses were fixed at 1.25 MIU/m2 and administered subcutaneously (SQ) on a daily basis with "intermediate-dose" pulses of 15 MIU/m^2/day for 3 days every two weeks. Fleming et al. teaches the

antibody was administered intravenously (IV) every two weeks prior to "intermediate-dose pulses". Fleming et al. teaches escalation of the dose of the antibody, which included doses of 1, 2, and 4 mg/kg. Fleming et al. disclosed no toxicity related to the antibody, but they found dose-limited toxicity associated with IL-2. Fleming et al. teaches reducing the dose of IL-2 to 1 MIU/m^2 daily with 12 MIU/m^2 pulses, which was well tolerated. Fleming et al. teaches complete response and partial responses in three patients treated with 4 mg/kg doses of the antibody, all of which were afflicted with breast cancer characterized by overexpression of HER2; no objective clinical response was observed in the two patients afflicted with other types of cancer (i.e., head and neck cancer, ovarian cancer). Fleming et al. teaches no objective clinical response was observed in any of the patients when the dose of the antibody was less than 4 mg/kg.

Fleming et al. does not expressly disclose that the recombinant anti-HER2 monoclonal antibody administered to the patients is a humanized form of murine antibody 4D5. Nonetheless, as evidenced by Fleming et al. (2002), the antibody administered in this phase I trial was Herceptin™, which the specification discloses is a humanized form of murine antibody 4D5 that binds the extracellular domain of HER2; see, e.g., page 3720, column 1. As a humanized antibody, Herceptin™ comprises at least one human constant region.

Fleming et al. does not expressly disclose the therapeutically effective dose of IL-2 is "administered as" a lyophilized pharmaceutical composition. While it is unlikely that a pharmaceutical composition would be "administered as" a lyophilized formulation, as evidenced by Fleming et al. (2002), IL-2 was supplied as a lyophilized cake in vials and was reconstituted in sterile water for injection; see, e.g., page 3720, column 1.

Claim Rejections - 35 USC § 103

17. Claims 27-31, 53, and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fleming et al. (Abstract No. 710, Program Proceedings, American Society of Clinical Oncology, 35th Annual Meeting, 1999) (of record), as evidenced by Fleming et al. (*Clin. Cancer Res.* 2002 Dec; **8**: 3718-3727), in view of Meropol et al. (*Cancer Immunol. Immunother.* 1998; **46**: 318-326).

Fleming et al. teaches that which is set forth in the above rejection of claims 12-15, 17, 22-26, 35-37, 51, 52, 57, 58, 63, 64, 66, 68, and 73 under 35 U.S.C. §102(b).

Fleming et al. does not expressly teach administering "recombinant" IL-2.

Nevertheless, Meropol et al. teaches aldesleukin, or Proleukin™; see entire document (e.g., page 319, column 1). Meropol et al. teaches such "recombinant" IL-2 is well tolerated and effective to stimulate expansion of natural killer cells over a prolonged course of treatment. Meropol et al. teaches as a next step in developing their program, they are undertaking a study combining daily subcutaneous administered low-dose IL-2, intermediate-dose pulses, and a humanized anti-HER2 monoclonal antibody in patients with cancers that overexpress HER2 (page 325, column 1).

Aldesleukin is "recombinant" IL-2, otherwise designated "des-alanyl-1, serine-125 human IL-2"; see, e.g., the specification, page 29, lines 1-11(as originally filed).

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have administered "recombinant" IL-2, or more particularly "des-alanyl-1, serine-125 human IL-2" (i.e., aldesleukin) together with Herceptin™ in practicing the process disclosed by Fleming et al. because Meropol et al. teaches such "recombinant" IL-2 is well-tolerated and effective to stimulate expansion of natural killer cells over a prolonged course of treatment, and moreover because Meropol et al. discloses studies using such a combination to treat patients afflicted with cancer characterized by overexpression of HER2 are already being undertaken. One ordinarily skilled in the art at the time the invention was made would have been motivated to do so to treat patients afflicted with breast cancer characterized by overexpression of HER2.

18. Claims 27-31, 53, 59, and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fleming et al. (Abstract No. 710, Program Proceedings, American Society of Clinical Oncology, 35th Annual Meeting, 1999) (of record), as evidenced by Fleming et al. (*Clin. Cancer Res.* 2002 Dec; **8**: 3718-3727), in view of U.S. Patent No. 4,863,726 A (of record).

Fleming et al. teaches that which is set forth in the above rejection of claims 12-15, 17, 22-26, 35-37, 51, 52, 57, 58, 63, 64, 66, 68, and 73 under 35 U.S.C. §102(b).

Fleming et al. does not expressly teach administering "recombinant" IL-2.

Nevertheless, U.S. Patent No. 4,863,726 A (Stevens et al.) teaches that which is set forth in the preceding Office actions[5]; see entire document. In particular, Stevens et al. teaches a "recombinant" IL-2, which is designated "des-ala$_1$-IL-2$_{ser}$125 mutein"; see, e.g., column 8, lines 46-55; column 24, lines 50-61. Furthermore, Stevens et al. teaches monoclonal antibody 520C9, which is used to make an immunotoxin effective in combination with recombinant IL-2 to treat mice bearing tumor cells to which the antibody binds; see, e.g., columns 23-25, Example II.

Absent a showing otherwise, the "recombinant" IL-2 disclosed by Stevens et al. is the "des-alanyl-1, serine-125 human IL-2" to which the claims refer.

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have administered "recombinant" IL-2, or more particularly "des-alanyl-1, serine-125 human IL-2" (i.e., "des-ala$_1$-IL-2$_{ser}$125 mutein") in practicing the process disclosed by Fleming et al. because Stevens et al. teaches such "recombinant" IL-2, when used in combination with antitumor monoclonal antibodies to treat patients afflicted with tumors to which the antibodies bind, is effective to cause tumor reduction and/or augment LAK activity and moreover it was well appreciated in the art at the time the invention was made that "recombinant" IL-2 is, for example, more cost-effectively prepared than non-recombinant IL-2. In addition, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have administered "recombinant" IL-2, or more particularly "des-alanyl-1, serine-125 human IL-2" (i.e., "des-ala$_1$-IL-2$_{ser}$125 mutein") in combination with an effective amount of an immunotoxin comprised of a humanized form of monoclonal antibody 520C9, as opposed to Herceptin™, because using an animal model Stevens et al. teaches the combination of such "recombinant" IL-2 and an immunotoxin comprised of the murine monoclonal antibody 520C9 is effective to treat tumors to which the antibody binds, and

because Fleming et al. teaches administering humanized antibodies, as opposed to murine antibodies to patients, as it was well appreciated by one ordinarily skilled in the art at the time the invention was made that humanized antibodies are used preferentially in treating patients because they are less immunogenic than murine antibodies and can therefore be administered more safely to humans without the risk associated with administering murine antibodies. One ordinarily skilled in the art at the time the invention was made would have been motivated to do so to treat patients afflicted with breast tumors to which the immunotoxin comprised of the humanized.

19. Claims 16, 32-34, 54, 55, 56, and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fleming et al. (Abstract No. 710, Program Proceedings, American Society of Clinical Oncology, 35th Annual Meeting, 1999) (of record), as evidenced by Fleming et al. (*Clin. Cancer Res.* 2002 Dec; **8**: 3718-3727), in view of U.S. Patent Application Publication No. 2003/0185796 A1.

Fleming et al. teaches that which is set forth in the above rejection of claims 12-15, 17, 22-26, 35-37, 51, 52, 57, 58, 63, 64, 66, 68, and 73 under 35 U.S.C. §102(b).

In particular, Fleming et al. teaches administering Herceptin™ every two weeks prior to "intermediate-dose" pulses of IL-2, which are administered for 3 days every two weeks to activate effector cells.

Fleming et al., however, does not expressly teach administering the antibody within 6 days of the initiation of a treatment period, as recited in claims 16 and 67.

U.S. Patent Application Publication No. 2003/0185796 A1 (Wolin et al.) teaches administering an anticancer monoclonal antibody in combination with IL-2; see entire document (e.g., the abstract). Wolin et al. teaches the dosing and scheduling can vary, so long as the treatment regimen provides beneficial therapeutic effects; see, e.g., paragraph [0017]; and paragraphs [0026]-[0062]. For example, Wolin et al. teaches multiple treatment cycles of variable duration to maintain NK cell count above an acceptable threshold level, wherein the duration of IL-2 administration is a function of

[5] See, e.g., the Office action mailed March 14, 2003, section 20, beginning at page 16; and the Office

the IL-2 dosing regimen used; see, e.g., paragraphs [0017], [0035], [0039], and [0116]. Wolin et al. teaches initial and subsequent treatment cycles are not necessarily the same; see, e.g., paragraph [0054]. Wolin et al. teaches both IL-2 and the antibody are administered concurrently on the same day, either at the same time (i.e., simultaneous administration) or at different times (i.e., sequential administration, in either order), or sequentially on different days; see, e.g., paragraph [0033]. At paragraph [0032], Wolin et al. teaches:

> [T]he two-level IL-2 dosing regimen is initiated prior to initiating weekly administration of therapeutically effective doses of anti-CD20 antibody. In this manner, a first dose of IL-2 is administered up to one month before the first dose of anti-CD20 antibody is administered. By "up to one month" is intended the first dose of IL-2 is administered at least one day before initiating anti-CD20 antibody administration, but not more than one month (i.e., 30 days) before initiating anti-CD20 antibody administration. Thus, IL-2 administration can begin, for example, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days (i.e., 1 week), 10 days, 14 days (i.e., two weeks), 17 days, 21 days (i.e., 3 weeks), 24 days, 28 days (4 weeks), or up to one month (i.e., 30 days) before administering the first therapeutically effective dose of the anti-CD20 antibody.

At paragraph [0018], Wolin et al. teaches, "[a]dministering of these two agents together in the manner set forth herein provides for greater therapeutic effectiveness than can be achieved using either of these agents alone, resulting in a positive therapeutic response that is improved with respect to that observed with either agent alone" and "the beneficial therapeutic effects of these agents can be achieved using lower cumulative dosages of IL-2, thereby lessening the toxicity of prolonged IL-2 administration and the potential for tumor escape". Wolin et al. teaches recombinant IL-2 is administered (e.g., Proleukin™); see, e.g., paragraphs [0056]-[0059]. In addition, Wolin et al. teaches different preparations of IL-2 may be formulated for use, including, for example, stabilized monomeric preparations and spray-dried preparations; see, e.g., paragraphs [0096]-[0100].

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have administered Herceptin™ to the patient following the initiation of a treatment period on any day preceding the administration of the first "intermediate-dose" pulse, since Wolin et al. teaches combining a two-level IL-2 dosing

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action mailed February 18, 2005, section 14, beginning at page 19, and section 15, beginning at page 22.

regimen and an anticancer antibody dosing regimen in which the IL-2 dosing regimen begins at, for example, 1 day, 2 days, 3 days, 4 days, 5 days, or 6 days before administering the first dose of the antibody. One ordinarily skilled in the art would have been motivated at the time the invention was made to practice the process disclosed by Fleming et al. by administering the antibody within, for example, 6 days of administering the first dose of IL-2 to the patient, so as to determine which schedule provides maximum therapeutic effect and/or optimal efficacy.

20. Claims 18, 19, 38-40, 42-47, 60-62, 69, and 70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fleming et al. (Abstract No. 710, Program Proceedings, American Society of Clinical Oncology, 35th Annual Meeting, 1999) (of record), as evidenced by Fleming et al. (*Clin. Cancer Res.* 2002 Dec; **8**: 3718-3727), in view of U.S. Patent Application Publication No. 2003/0185796 A1, as applied to claims 16, 32-34, 54, 55, and 67 above, and further in view of Sosman et al. (*J. Clin. Oncol.* 1993 Aug; **11** (8): 1496-1505).

Fleming et al. teaches that which is set forth in the above rejection of claims 12-15, 17, 22-26, 35-37, 51, 52, 57, 58, 63, 64, 66, 68, and 73 under 35 U.S.C. §102(b).

U.S. Patent Application Publication No. 2003/0185796 A1 (Wolin et al.) teaches that which is set forth in the above rejection of claims 16, 32-34, 54, 55, and 67 are rejected under 35 U.S.C. 103(a).

However, none of the aforementioned references expressly teaches administering the antibody and IL-2 during an "introductory cycle", *per se*, which comprises daily administration of IL-2 through at least day 20 of the cycle and the administration of the antibody on day 7 of the cycle, as recited in claims 18, 42, and 69. Furthermore, none of the aforementioned references expressly teaches cycles of treatment that occur subsequently to such an "introductory cycle", which comprises administration of the antibody at day 1 and daily administration of IL-2 through at least day 14, as recited in claims 19, 47, and 70.

Sosman et al. teaches a phase I clinical trial combining monoclonal antibody therapy and IL-2 therapy in which patients were initially treated during a 20-day cycle; see entire document (e.g., the abstract).

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have administered Herceptin™ to the patient following the initiation of an "introductory cycle" of treatment lasting at least 20 days, which comprises administering IL-2 daily and administering the antibody on day 7 of the cycle, preceding the administration of the first "intermediate-dose" pulse, since Wolin et al. teaches combining IL-2 therapy with antibody therapy during variable courses of an extended multicycle treatment regimens, which are adjusted so as to provide maximum therapeutic effect and/or optimal efficacy, and Sosman teaches an initial or "introductory" cycle of 20 days, which similarly comprises administering an antibody and IL-2. Furthermore, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have followed such an "introductory" treatment cycle with subsequent cycles of at least 14 days comprising administering the antibody on the first day of the cycle and administering IL-2 daily, since Wolin et al. teaches treatment regimens comprising multiple cycles, which are not necessarily the same, and may comprise administering the antibody on the first day of such a cycle and administering IL-2 on a daily basis for periods of, for example, two weeks. One ordinarily skilled in the art would have been motivated at the time the invention was made to practice the process disclosed by Fleming et al. by administering the antibody on day 7 of, for example, an initial treatment cycle of at least a 20 days comprising daily administrations of IL-2 to the patient, just preceding the administration of the first "intermediate-dose" pulse of IL-2, and then follow such an initial treatment cycle with subsequent treatment cycles comprising administering the antibody on the first day and administering IL-2 daily, so as to determine whether such a schedule provides maximum therapeutic effect and/or optimal efficacy.

21. Claims 20, 21, 41, 48-50, 71, and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fleming et al. (Abstract No. 710, Program Proceedings,

American Society of Clinical Oncology, 35th Annual Meeting, 1999) (of record), as evidenced by Fleming et al. (*Clin. Cancer Res.* 2002 Dec; **8**: 3718-3727), in view of U.S. Patent Application Publication No. 2003/0185796 A1 and Sosman et al. (*J. Clin. Oncol.* 1993 Aug; **11** (8): 1496-1505), as applied to claims 18 and 19 above, and further in view of Soiffer et al. (*Clin. Cancer Res.* 1996 Mar; **2** (3): 493-499).

Fleming et al. teaches that which is set forth in the above rejection of claims 12-15, 17, 22-26, 35-37, 51, 52, 57, 58, 63, 64, 66, 68, and 73 under 35 U.S.C. §102(b). In particular, it is noted that Fleming et al. teaches a regimen comprising daily administration of low-dose IL-2 followed by "intermediate-dose" pulses for 3 days every two weeks.

U.S. Patent Application Publication No. 2003/0185796 A1 (Wolin et al.) teaches that which is set forth in the above rejection of claims16, 32-34, 54, 55, and 67 are rejected under 35 U.S.C. 103(a).

Sosman et al. teaches that which is set forth in the above rejection of claims 18 and 19 are rejected under 35 U.S.C. 103(a).

However, none of the aforementioned references expressly teaches weekly administration of "intermediate-dose" pulses of IL-2 during the "introductory cycle" of at least 20 days on days 8-10, or during subsequent cycles of at least 14 days on days 1-3, as recited in claims 20, 21, 41, 48-50, 71, and/or 72.

Soiffer et al. teaches a regimen comprising an introductory "priming" cycle of daily administration of low-dose IL-2 followed by "intermediate-dose" pulses (i.e., boluses) for 5 days every week; see entire document (e.g., the abstract; and page 494, Figure 1).

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have administered Herceptin™ to the patient following the initiation of an "introductory cycle" of treatment lasting at least 20 days, which comprises administering IL-2 daily and administering the antibody on day 7 of the cycle, preceding the administration of the first of three daily "intermediate-dose" pulses of IL-2 beginning on day 8 of the cycle, since Fleming et al. teaches a regimen comprising daily administration of low-dose IL-2 followed by "intermediate-dose" pulses for 3 days every

two weeks, whereas Soiffer et al. teaches a regimen comprising an introductory "priming" cycle of daily administration of low-dose IL-2 followed by "intermediate-dose" pulses (i.e., boluses) for 5 days every week. Furthermore, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have followed such an "introductory" treatment cycle with subsequent cycles of at least 14 days comprising administering the antibody on the first day of the cycle, administering "intermediate-dose" pulses of IL-2 on days 1-3 of the cycle, and then after administering "low-dose" IL-2 daily, since, again, Fleming et al. teaches a regimen comprising daily administration of low-dose IL-2 followed by "intermediate-dose" pulses for 3 days every two weeks, Soiffer et al. teaches a regimen comprising an introductory "priming" cycle of daily administration of low-dose IL-2 followed by "intermediate-dose" pulses (i.e., boluses) for 5 days every week, and Wolin et al. teaches treatment regimens comprising multiple cycles, which are not necessarily the same, and may comprise administering the antibody and IL-2 on the first day of such a cycle. One ordinarily skilled in the art would have been motivated at the time the invention was made to do so in order to determine whether such a schedule provides maximum therapeutic effect and/or optimal efficacy.

Conclusion

22. No claim is allowed.

23. As first noted in section 19 of the preceding Office action, Applicant is again advised that should claims 18 and 38-40 be found allowable, claims 43-46 will be objected to under 37 CFR § 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

24. The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. Kawase et al. (*Cancer Res.* 1988 Mar 1; **48** (5): 1173-1179), Vuist et al. (*Cancer Res.* 1990 Sep 15; **50** (18): 5767-5772), and Caron et al. (*Clin. Cancer Res.* 1995 Jan; **1** (1): 63-70) teach the combination of IL-2 and antitumor monoclonal antibodies capable of inducing ADCC. Cooley et al. (*Exp. Hematol.* 1999 Oct; **27** (10): 1533-1541) suggests combining Herceptin™ and IL-2. Soiffer et al. (*Clin. Cancer Res.* 1997 Jan; **3** (1): 17-24), Keilholz et al. (*Leuk. Lymphoma.* 1999 Nov; **35** (5-6): 641-642), and Kossman et al. (*Clin. Cancer Res.* 1999 Oct; **5**: 2748-2755) teach combining a monoclonal antibody and IL-2. Weiner et al. (*J. Hematother.* 1995 Oct; **4** (5): 453-456) (of record) teaches combining a bispecific antibody that specifically targets tumor cells expressing HER2, which also binds natural killer cells expressing CD16, and IL-2. Skog et al. (*Cancer Immunol. Immunother.* 1999 Nov; **48** (8): 463-470) teaches a treatment regimen that combines monoclonal antibody therapy with cytokine (i.e., IL-2 and GM-CSF) therapy, wherein the antibody is administered at day 3 of a 10-day treatment cycle, and the cytokines are administered daily. Vlasveld et al. (*Cancer Immunol. Immunother.* 1995 Jan; **40** (1): 37-47) teaches a treatment regimen that combines monoclonal antibody therapy with IL-2 therapy, wherein the antibody is administered twice weekly, and IL-2 is administered continually. Chachoua et al. (*J. Immunother. Emphasis Tumor Immunol.* 1994 Aug; 16 (2): 132-141) teaches a 21-day cycle of treatment, which combines administering a monoclonal antibody with daily administration of GM-CSF. Caligiuri et al. (*J. Clin. Invest.* 1993 Jan; **91**: 123-132) teaches selective modulation of natural killer cells *in vivo* after prolonged treatment with low dose recombinant IL-2. Baselga et al. (*Semin. Oncol.* 1999 Aug; **26** (4 Suppl. 12): 78-83) reviews the results of phase II clinical trial of trastuzumab.

Though not prior art, it is noted U.S. Patent Application Publication No. 2003/0235556 A1 teaches combining anti-HER2 antibody therapy and IL-2 therapy. Additionally, Repka et al. (*Clin. Cancer Res.* 2003 Jul; **9**: 2440-2446) teaches a pilot study of the combination of trastuzumab and IL-2 in treating breast cancer.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1643

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February 15, 2006